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(54) Title: COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER

(57) Abstract

A spray applicator is disclosed for administering an opioid antagonist selected from naloxone and/or naltrexone. The applicator is capable of delivering single or multiple doses of the antagonist through a projecting delivery portion which is shaped or dimensioned for introduction into the nose or mouth. A pharmaceutical composition for nasal or oral administration is also disclosed which comprises an opioid antagonist, such as naloxone and/or naltrexone, and which comprises a water–susceptible solid carrier admixed with the opioid antagonist.

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COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER

This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage.

Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation.

The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage.

According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient.

According to another aspect of the invention there is provided a pharmaceutical composition for oral or nasal administration comprising an opioid antagonist, the composition being in finely-divided solid form and comprising a water-susceptible solid carrier and the opioid antagonist.

The spray applicator may be designed for dispensing the solution into the mouth, e.g. sub-lingually, and be provided with a projecting delivery portion for this purpose. However, in a preferred embodiment, the applicator has a delivery portion which is shaped and dimensioned for introduction into a nostril so that the dose is sprayed directly into the nasal passages. The latter mention of administration may be more convenient and enables resuscitation to be continuously and simultaneously applied. Also, a device which has such a projecting delivery portion can also, if appropriate, be applied directly into the mouth.

Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle.

According to the aspect of the invention in which the pharmaceutical composition is in powder form, it is preferably administered nasally. In this embodiment, the composition is packaged via a dispenser having a projecting portion for introduction into a nostril. Normally, a propellant is employed for generating an aerosol of the powdered pharmaceutical in a stream of gas. The dispenser will generally include means for metering doses of the composition dispensed into the patient's nasal passages.

A preferred opioid antagonist for use in the compositions of this invention is naloxone, which is:-

17-allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine.

Another example of an opioid antagonist is naltrexone, which is:-

17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

A mixture of two or more opioid antagonists may be employed. Preferably, naloxone is used as a sprayable liquid composition and naltrexone is preferably used in the form of a powdered, solid composition, usually for nasal administration.

Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution. A concentration of about 0.9 weight/volume NaCl in purified water is suitable. The composition may include a buffering agent to maintain the opioid in solution in the salt form, e.g. a phosphate buffer, such as sodium hydrogen phosphate to maintain the solution at a slightly acid pH. A solution of the antagonist, usually in the form of the hydrochloride, at a concentration of from about 0.5 to 5% by weight, preferably about 1 to 2%, may be employed for nasal or buccal administration. The

liquid composition may be packaged in a metered dosage spray dispenser, using a pump or propellant. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µl and 100µl, with the dose per shot preferably varying between 200 and 1200µg.

In the case of a solid, powdered composition for nasal administration, the antagonist is mixed with one or more solid, powdered carriers. Suitable carriers include saccharides such as sorbitol, mannitol, lactose, fructose, glucose and sucrose. Other carriers include water-soluble or swellable polymers such as cellulose derivatives, for example, hydroxypropyl methyl cellulose and carboxymethyl cellulose. A solid salt of the antagonist, e.g. the hydrochloride, maybe mixed with a carrier, or coated with the carrier or with a third material such as a hydrophilic polymer.

Solid, powdered formulations generally are dispensed at a total shot weight of about 20mg, giving a naloxone dose of 400µg per shot. Typical total shot weights may vary between about 10 mg and 30mg and the naloxone dose per shot may be between about 200 and 1200µg.

The solid, powdered composition containing the opioid antagonist may be packaged in a dispenser with a suitable propellant, such as HFC-134a or HFC-227. Again, a valve may be provided, which is adapted to dispense a dosage unit of the antagonist of about 0.2 to 5 mg, e.g. 0.4 to 2mg preferably 0.4 to 1.2mg.

It may be desirable to include an anti-oxidant, such as ascorbic acid or citric acid in the powdered formulation.

The invention is illustrated by the following Examples of pharmaceutical compositions suitable for use in dispensing the opioid antagonist and by the accompanying drawing and description of one form of spray applicator suitable for dispensing the liquid composition.

Example 1

Sprayable aqueous liquid composition for a nasal applicator.

Naloxone hydrochloride was dissolved in a solution of purified water to form a solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was

added to the hydrochloride solution in an amount of 0.025% weight/volume as a preservative. The solution may be buffered to a pH of about 6.5 using a phosphate buffer (sodium or potassium hydrogen phosphate). The solution was packaged into a dispenser as shown in the accompanying drawing, giving a shot volume of 50µl (microlitre) which is equivalent to a unit dose of 400µg (microgram) per shot.

Example 2

Solid, powdered nasal preparation.

Powdered solid naloxone hydrochloride was mixed with powdered dextrose or lactose in an amount of from 2% weight/volume naloxone HCl and 98% weight/volume of the finely powdered sugar. The resulting mixture may be subsequently coated with a vinyl pyrollidone to form a free-flowing powder in which the opioid antagonist is present in a concentration of 2% by weight. The powdered composition was packaged in a dispenser as described in WO 99/27920.

Example 3

Naloxone HCl was dissolved in water with mannitol or lactose in a weight ratio of 2:98. The resulting solution was spray dried or freeze dried to form a fine powder containing 2% of naloxone HCl.

The powdered product could be packaged in an aerosol can with a low boiling propellant fitted with a metering valve or in a dispenser as described in WO 99/27920.

The accompanying drawing is a perspective view of an applicator suitable for dispensing liquid solutions of the opioid antagonist.

Referring to the drawing, the applicator 1 is shown in its assembled state in Figure 1. Figure 1a is a perspective view of a cover cap and Figure 2 is a perspective view of the reservoir 2 and piston 3.

The applicator comprises a body part 4 moulded from a flexible plastics material and having a projecting part 5 suitably sized for insertion into a nostril. The projecting part 5 has an internal tube 6 (shown in broken lines in Figure 1), which

extends from the tip 7 to approximately the junction between part 5 and the main body part 8. At its distal end, tube 6 is joined to the inside of the projecting part 5, e.g. by forming part of an integral moulding, and communicates with a discharge orifice 9.

A solution of the drug to be dispensed is contained in reservoir 2 which is preferably made from transparent plastic or glass so that it can be seen by inspection if it contains any drug. For this purpose, the solution may be coloured with a pharmaceutically acceptable dye.

Piston 3 is made from flexible plastics material (e.g. polythene) and carries a solid piston rod 10 which is formed with a passage 11. Passage 11 communicates with the interior of the reservoir and terminates in a cross bore 12. The assembly consisting of the reservoir 2 and piston 3 and piston rod 10 are fitted into the body 4 of the applicator by introducing the rod 10 into the tube 6. Rod 10 is a free fit into the part of the tube 6 nearest to the part 8 but is a tighter fit into the distal end of the tube. The device works as follows. With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6. Tube 6 may be tapered slightly towards the orifice so that higher pressure can be developed within its distal end. It will be appreciated that by shaping the projecting part 5 as a tapering fit in the nostril, a major amount of the composition is retained in the nasal passages.

Figure 1a shows a cap 20 for fitting over the part 5 and maintaining it clean prior to use. Cap 20 may be a snap fit onto the base of the projecting part 5 and incorporates a shroud 21 which seals onto the distal end of the part 5.

The compositions of the invention have the advantage that they can be administered by a first-aider or person having no medical training, such as a friend or neighbour of an addict. A single dose of the antagonist can readily be sprayed into the nose or mouth of an addict who is having difficulty breathing, while undertaking standard resuscitation procedures. If the patient does not respond to the initial dose,

further doses of the antagonist can be given until reversal of the opioid depression is apparent. An advantage is that treatment can be given quickly and effectively without the need for the first-aider to find a blood vessel and give an intravenous injection. Another advantage of the applicators of the invention is that they cannot be misused to give injections of other drugs and are thus more likely to be retained and used for their intended purpose.

CLAIMS:-

1. A spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient.

2. Applicator according to claim 1 wherein the solution is an aqueous solution of the opioid antagonist.

3. Applicator according to claim 2 wherein the solution includes a buffer in an amount sufficient to maintain a pH at which the antagonist is in the form of a pharmaceutically acceptable salt.

4. Applicator according to any one of the preceding claims in which the antagonist is present in the solution in an amount of from 0.5 to 5% by weight.

5. Applicator according to any one of the preceding claims wherein each said dose comprises from 0.4 to 3 mg of the antagonist.

6. Applicator according to any one of the preceding claims which comprises a pump action dispenser.

7. A pharmaceutical composition for nasal or oral administration which comprises an opioid antagonist, the composition being in finely-divided solid form and comprising a water-susceptible solid carrier and the opioid antagonist.

8. A composition as claimed in claim 7 wherein the antagonist is naloxone and/or naltrexone.

9. A composition as claimed in claim 7 or 8 which includes a hydrophilic polymer.

10. A composition as claimed in claim 9 in which the antagonist is mixed with the carrier and the mixture coated with a hydrophilic polymer.

11. A composition as claimed in any one of claims 7 to 10 in which the antagonist is present in an amount of from about 0.5 to 5% by weight of the total composition.

12. A composition as claimed in any one of claims 7 to 11 which is packaged in a dispenser capable of delivering a metered dose of the composition into the nose.

13. A composition as claimed in claim 12 wherein the metered dose is from 0.4 to 2 mg.

14. A composition as claimed in claim 12 or 13 wherein the dispenser includes an aerosol propellant.

15. A composition as claimed in claim 15 wherein the propellant is a hydrofluorocarbon.

16. Use of a spray applicator as claimed in any one of claims 1 to 6 in the manufacture of a device for reviving a person suffering from opioid overdose.

17. Use of a composition as claimed in any one of claims 8 to 15 in the manufacture of a pharmaceutical for reviving a person suffering from opioid overdose.

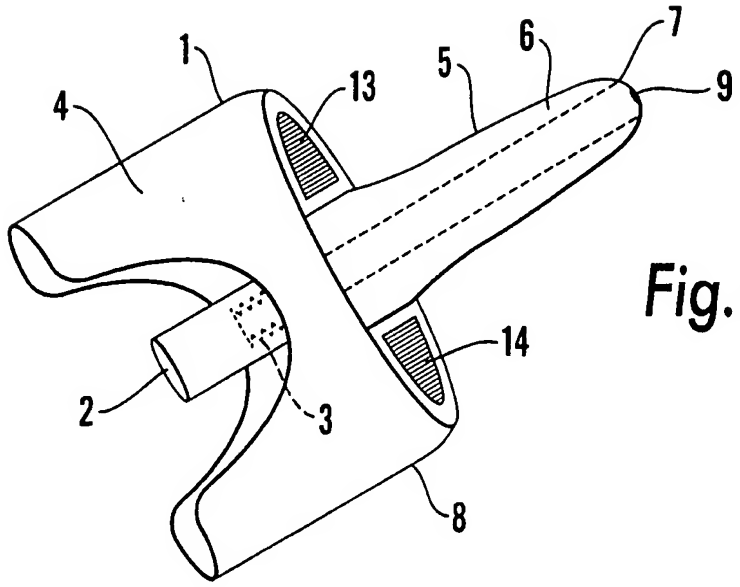

Fig. 1

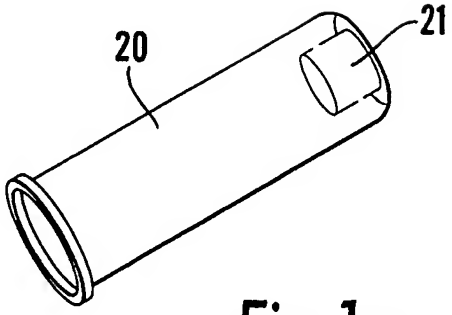

Fig. 1a

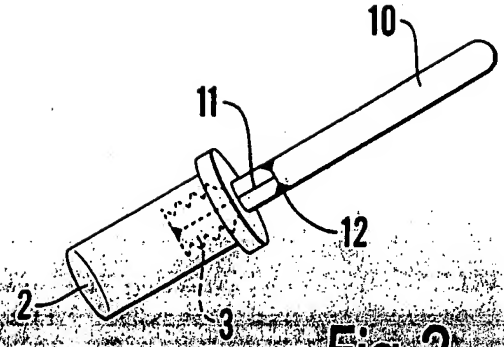

Fig. 2

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/GB 00/01509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K31/485 A61M15/08 A61P25/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 464 378 A (A. A. HUSSAIN) 7 August 1984 (1984-08-07) claims 1-14,36-46 column 9, line 16 - line 39	1-6,16, 17
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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